Clinics in Dermatology (2019) **37**, 548–560

Clinics in Dermatology

The color of skin: red diseases of the skin, nails, and mucosa

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Abstract Red color is pervasive in local and systemic skin conditions. It is a color that often reflects variations of dermal blood flow and extends beyond the *rubor* and *calor* of inflammation. The pathophysiology of red skin involves remote and local chemical mediators that dilate arteriolar smooth muscle and increase blood flow to superficial vessels and capillary beds. Incident light hits hemoglobin, which preferentially absorbs light of shorter wavelengths, such as blue, and reflects warmer colors. Due to its pervasiveness and consistency, red color is a useful descriptive factor in helping narrow a differential diagnosis. Red skin disorders include a variety of conditions involving endocrine mediators, cardiovascular responses, and the disruption of the skin barrier. An understanding of the blood's role in these disorders equips clinicians to generate differential diagnoses through the lens of pathophysiology. Dermatologists can improve management by considering red skin as part of systemic disease rather than as an isolated incident.

Introduction

It is difficult to find a color more prevalent in skin conditions than red. Often, pathophysiology involves vasodilation and an increased concentration of dermal blood, causing the *rubor* and *calor* of inflammation or the rosy glow of an embarrassed face. A red "Rudolph" nose can occur after stepping inside from cold weather when the constricted vessels in the nasal tip finally relax, or a red nose can be more permanent as in rhinophyma. Few colors represent such a variety of conditions as red. The color red is also an identifier. "Redskin" is a pejorative racial identifier for Native Americans, yet the term does not accurately describe the skin color of these peoples, whose skin tone has also been characterized as "brown" and "olive."[1] Red conditions differ based on the Fitzpatrick skin type, with dark skin imbuing a duskier, violaceous hue to classically red diseases. Subtle differences also characterize similar conditions such as the transient red face of blushing and flushing. The milder blushing is generally restricted to the cheeks, ears, or face and usually reflects an emotional response. Flushing causes a marked red hue in the face and often on other body parts due to a physical stress (eg, alcohol consumption, histamine/serotonin release in carcinoid syndrome, or exercise).

Red color, with the longest wavelength on the visible spectrum, represents 620 to 750 nm light. Red is a primary color next to orange and is the opposite of violet; green is its complementary color.[2] The red color of autumn leaves and apples

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https://doi.org/10.1016/j.clindermatol.2019.07.017
0738-081X/

contain anthocyanins; the color of blood comes from oxyhemoglobin, which absorbs short wavelengths strongly.[3] Deoxygenated blood in veins still reflects red light, although venous blood appears duskier than arterial blood due to the conformational changes of deoxygenated hemoglobin.[4,5] In this review on red diseases, we describe a spectrum of clinical appearances for an overview of each disorder.

Definition

The color red is defined by its presence on the visible spectrum, ranging from 620 to 750 nm; however, we define red diseases more clinically, as physicians consistently use color to describe dermatologic lesions.[6] We consider red diseases as those that classically appear red as a primary lesion or are associated with a background of red (eg, erythema), as seen in the example of secondary impetigo in Figure 1. We define erythema as a superficial, blanchable redness of the skin created by dilated blood vessels. In addition, we focus on red diseases of the adult population; although diseases that commonly affect pediatric patients will be discussed, they are not the focus of this review. Red diseases can be grouped into two major categories: primary and secondary.

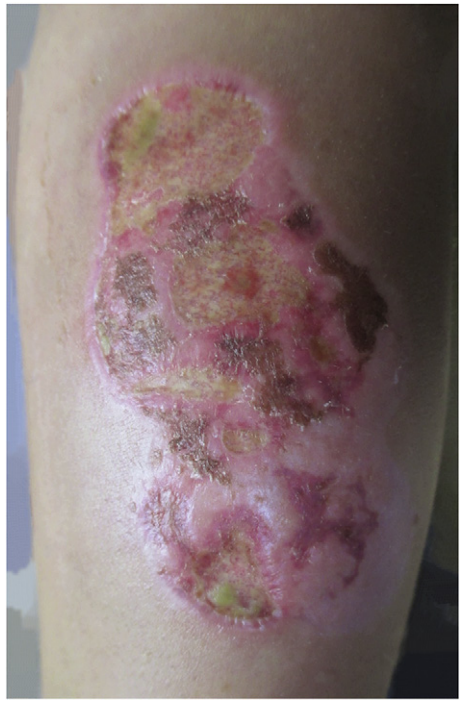

Fig. 1 An example of a honey-colored crusted ulceration on an erythematous base, showing a secondarily infected ulceration of impetigo.

Primary disease

Atopic dermatitis

Atopic dermatitis is a chronic relapsing inflammatory dermatologic condition. There are many proposed etiologies of atopic dermatitis, with a possible genetic factor that affects both epidermal barrier function and immune response. One suggested etiology involves the disruption of the epidermal barrier by a filaggrin gene mutation, leading to xerosis and introduction of antigens and irritants into the skin.[7] Patients with atopic dermatitis have decreased cell-mediated immunity. Severe cases can show elevated IgE levels, which is a marker for decreased regulatory T-cell levels and disrupted immune regulation.[8,9] Pruritis is the overwhelming symptom. Typically, infants present with papules and vesicles on the head/neck, extensor surfaces, and groin areas.[10] Children present with scaly and chronic lichenified plaques on the face and flexural surfaces, and adults present with similar lesions on the torso and hands.[10]

The differential diagnosis of atopic dermatitis includes contact dermatitis, scabies, and, in cases where lesions appear well-defined, psoriasis. Because the diagnosis is clinical, a biopsy is rarely pursued and shows a nonspecific spongiotic dermatitis. Treatment should start with avoidance of known triggers and use of gentle moisturizers.[11] Patients with localized disease should start with topical corticosteroids to reduce flare-ups and can be maintained on topical calcineurin inhibitors such as tacrolimus.[11] In older children or adults with moderate to severe cases, phototherapy is an option. In adults with refractory disease, systemic immunosuppressive medications, such as oral cyclosporine or oral dupilumab, can be pursued.

Contact dermatitis

Contact dermatitis is a common cutaneous condition that involves a localized inflammatory reaction to chemical or physical agents; the two major types of contact dermatitis are allergic and irritant. Allergic contact dermatitis reactions start with a T-cell mediated induction phase, which sensitizes the immune system; afterward, the reaction enters the elicitation phase, wherein a Type IV hypersensitivity reaction is triggered.[12] Irritant contact dermatitis involves disruption of the skin barrier, damage to keratinocytes, and release of inflammatory cytokines. Clinically, allergic and irritant contact dermatitis are similar. They manifest as erythematous, pruritic, indurated skin with or without scaly plaques, vesicles, bullae, and edema. Irritant contact dermatitis may present with fissures and more commonly arises on hands where it can coexist with pompholyx.[13] The differential diagnosis includes psoriasis, atopic dermatitis, seborrheic dermatitis, and fungal infections. Treatment begins with recognition of the clinical problem and identification of the source; for this, there is no substitute for a thorough history, examination, and patch

testing. Avoidance of the offending agents, restoring the skin barrier with emollients, and taming skin inflammation with corticosteroids are first-line options.

Red hair

Red hair is one of few examples wherein the color red does not connect to blood vessels. It is a rare recessive phenotype that has an estimated world prevalence of 1% to 2%. The color of red hair ranges from a bright strawberry blonde to a darker auburn. Red hair is genetically associated with mutations in the melanocortin 1 receptor (MC1R) gene.[14] These mutations create a predominance of pheomelanin, which is a cysteine derivative that causes the characteristic red hair appearance, over eumelanin. Patients usually have associated fair skin, freckles, ultraviolet light sensitivity, and an increased risk for both nonmelanoma skin cancer and melanoma.[14]

Rosacea

Rosacea is a chronic inflammatory condition of unknown etiology. There are many theories on the cause including UV photosensitive damage to collagen, Demodex mites, immunoglobulin deposition, and genetics.[15,16] Four major types exist[17]:

- erythematotelangiectatic
- papulopustular
- phymatous
- ocular

Rosacea presents with pustules, papules, or telangiectasias on a patch of erythema. Patients with any type of rosacea should use sunscreen and gentle skin care and be counseled on avoiding known triggers.[18] Often, individuals are counseled to limit the potential trigger of coffee, although a new women's study found those with higher coffee intake were less likely to develop rosacea.[19] More advanced management of erythema may involve the use of topical brimonidine (alpha-2 agonist), intense pulsed light, or a pulsed dye laser. In cases of papulopustular rosacea, topical metronidazole and azelaic acid are first-line interventions; for refractory or moderate-to-severe papulopustular disease, oral tetracyclines are the standard.[18,20]

Seborrheic dermatitis

Seborrheic dermatitis is a common chronic dermatitis that presents with scaly patches, typically on the face and scalp. Clinically, seborrheic dermatitis is often first evident as well-demarcated, erythematous plaques with greasy, yellow scales on the hair-bearing areas of the face or scalp or in the nasolabial folds. On the scalp, fine, white, diffuse scaliness is often present without underlying erythema.[21] The differential consists of psoriasis, rosacea, contact dermatitis, tinea versicolor, secondary syphilis, and systemic lupus erythematosus.

Hand dermatitis

Hand dermatitis is an umbrella term for an inflammatory condition that leads to skin breakdown and disruption of the epithelial barrier. There are many etiologies of hand dermatitis, including atopic dermatitis, allergic contact dermatitis, and irritant contact dermatitis.[22,23] Acute hand dermatitis presents with pruritic vesicles on an erythematous base. Hand dermatitis can lead to lichenification and skin fissuring. Irritant contact dermatitis usually presents on the hands or palms, whereas allergic contact dermatitis usually presents on the dorsum of fingers.[23] Treatment of hand dermatitis starts with the use of emollients and avoidance of known triggers.[23] Acutely, hand dermatitis can be treated with topical corticosteroids; however, if chronic therapy is required, topical calcineurin inhibitors, phototherapy, or a retinoid can be options.[23]

Rubronychia

Rubronychia, as seen in Figure 2, is a ruby red color of some or all the nail plates of the fingers or toes, although the lunula may remain normal in coloration.[24] It is an asymptomatic condition but may cause concern and emotional distress. Rubronychia needs to be distinguished from erythronychia, which may be evident as a red lunula with a pink thin column that extends through the nail bed to the nail tip.

Red splinter lines in nails

Splinter hemorrhages are red-black longitudinal lines under the nail plate, representing rupture of distal nail bed capillaries.[25] Although famously related to infective endocarditis, splinter lines are most commonly caused by trauma, along with nail psoriasis, lichen planus, renal failure, and various connective tissue disorders.[25–27] Trauma-related hemorrhages are often distal on the nail, whereas systemic diseases begin more proximally.

Cherry angiomas

Cherry angiomas, or Campbell de Morgan spots, are benign capillary proliferations common in middle-aged and older adults. The pathogenesis of such lesions is unknown, although oncogenic mutations of GNA11 and GNAQ—mutations found in Sturge-Weber syndrome—have been reported in 50% of cases in a recent study.[28] Cherry angiomas are less than 0.5 cm, dome-shaped red papules that blanch with pressure and can bleed with trauma. The differential must consider the malignant amelanotic melanoma, which would be friable on examination or have a history of evolution.[29] Biopsy is not needed. Treatment is not required, although clinicians

Fig. 2 Rubronychia: Multiple nails showing red coloration, predominantly in the distal aspect of the nail.

can remove cherry angiomas with electrocautery, cryotherapy, laser therapy, or shave excisions.[30]

Hemangiomas

Hemangiomas are the most common vascular tumors in infants and usually appear most often in the head/neck region within the first months of life.[31] They may be deep or superficial and range in size. Superficial hemangiomas are normally bright red, blanchable papules, nodules, or plaques. Deep (subcutaneous) hemangiomas are skin-colored nodules that often hold a bluish hue due to the scattering of blue light through the skin layers.[32] These lesions grow and proliferate for months, typically resolving over the course of years. The pathogenesis may be related to hypoxia, with the blood vessel proliferation representing a response to normalize hypoxic tissue.[33] This evidence stems from the associations of hemangiomas with utero hypoxia (eg, preterm or placental abnormalities). Biopsy and treatment are not necessary.

Secondary disease

Cellulitis

Cellulitis is an infection of the deep dermis and subcutaneous tissue that presents with skin erythema, edema, and warmth.[34] Predisposing risk factors include trauma, skin inflammation, lymphatic/venous insufficiency, immunosuppression, and obesity.[35,36] Like erysipelas, Group A streptococci cause the majority of cellulitis infections, although methicillin-sensitive *Staphylococcus aureus* (MSSA) or methicillin-resistant *Staphylococcus aureus* (MRSA) are also common culprits.[37] Less common causes of cellulitis include *Haemophilus influenzae* (buccal cellulitis), clostridia and anaerobes (crepitant cellulitis), *Streptococcus pneumoniae,* and *Neisseria meningitidis.*[38–40] Cellulitis is seen most often in middle-aged and older adults. Both purulent and nonpurulent cellulitis involve the deep dermis and subcutaneous tissue; in addition, both present with flat edges, unilaterally, poorly demarcated patches, and an indolent course with fever.[41] The differential includes necrotizing fasciitis, erythema migrans, septic arthritis/bursitis, herpes zoster, insect bites, and osteomyelitis. Treatment is with empiric antimicrobials covering MRSA and beta-hemolytic streptococci. If a drainable abscess is present, an incision and drainage, culture, and susceptibility testing are warranted.

Erysipelas

Erysipelas, a superficial subtype of cellulitis, manifests as skin erythema, edema, and warmth due to a bacterial infection of the superficial dermis. Infection due to Group A streptococcus is the most common cause. Erysipelas usually involves the face and, like cellulitis, is often unilateral and can involve the lower extremities.[42] Clinically, erysipelas presents with localized erythema but is actually a systemic disease. Patients often present with a rapid spread and onset of the nonpurulent infection, pyrexia early in the course, and raised, sharply demarcated edges of erythema.[43] Regional lymphadenopathy may be present, as well as lymphangitis, vesicles, bullae, ecchymoses, or petechiae. Systemic manifestations of fever, chills, malaise, and headache can precede the onset of local inflammatory signs/clinical manifestations by hours.[44] Classic descriptions of erysipelas include the involvement of the thin skin of the ear or a "butterfly" involvement of the face.[34] The diagnosis is clinical. Compared with cellulitis, erysipelas lacks the flat edges and poor demarcation, is more rapid in course, and does not present with delayed pyrexia.[41] Other diagnoses in the differential include toxic shock syndrome, necrotizing fasciitis, erythema migrans, septic arthritis, and allergic contact

dermatitis. When clinical diagnosis of erysipelas is made, treatment includes empiric antibiotic coverage for beta-hemolytic streptococci.[43]

Abscesses

A cutaneous abscess is most commonly caused by MSSA or MRSA.[45] Skin abscesses can also be polymicrobial, with colonization of *Sta aureus, Str pyogenes,* gram-negative bacilli, and anaerobes; these polymicrobial abscesses occur most commonly in the perioral, perirectal, or vulvovaginal areas.[46] Systemic clinical manifestations, including fever, chills, and malaise, are unusual[46]; however, carbuncles are more likely to have systemic clinical manifestations. The differential diagnosis includes epidermoid cyst, nodular lymphangitis, folliculitis, and, when in intertriginous skin, hidradenitis suppurativa. The primary treatment for skin abscesses, furuncles, and carbuncles is incision and drainage.[47,48] Antimicrobial recommendations vary but must cover MRSA if cultures do not rule it out. It is reasonable to forgo antibiotic therapy in healthy patients with small (<2 cm) abscesses.[49] Antimicrobial therapy is necessary for patients with multiple lesions, large abscesses (>2cm), extensive surrounding cellulitis, immunosuppression, systemic toxicity, or inadequate response to incision and drainage.[50]

Candidosis

General candidosis usually presents with vesicles that become confluent over an erythematous patch on the thorax or extremities.[51] Candidal intertrigo demonstrates large, erythematous patches with associated satellite vesicles and maceration in intertriginous areas (axilla, genitocrural folds, and gluteal folds).[51] The differential of candidal intertrigo includes noncandidal intertrigo (from a secondary bacterial infection), inverse psoriasis, and erythrasma. The presence of a few satellite papules or pustules is highly suggestive of candidal intertrigo, whereas the absence of these satellite lesions and a negative KOH preparation suggest another etiology. In addition, tinea cruris presents as an annular scaly plaque with sparing of the scrotum/penis and labia.

Pityriasis rosea

Pityriasis rosea (PR) is an acute inflammatory papulosquamous disorder that generally resolves within 1 to 3 months of onset.[52] Although the etiology is unclear, PR is a type IV hypersensitivity reaction possibly triggered by human herpesviruses (HHV) 6 and 7.[52,53] PR begins in 40% to 76% of patients with a single pink scaly plaque, known as a "herald patch."[52] This is followed by erythematous plaques with a collarette scale along the Langer lines of skin tension generally on the trunk; this eruption sometimes follows a "Christmas tree" distribution. The differential includes secondary syphilis, tinea corporis, guttate psoriasis, nummular dermatitis, pityriasis lichenoides chronica, and drug eruption. Secondary syphilis should be ruled out before the diagnosis of PR, especially if there is no history of a herald patch or if the palms and soles are involved. Biopsy is unnecessary and yields a nonspecific result with focal parakeratosis, spongiosis, acanthosis, and perivascular inflammation. Treatment for PR is unnecessary, as the disease is self-limiting, lasting about 6 weeks.[52] There is limited information on the effectiveness of acyclovir in hastening resolution of the disease, and it is not currently recommended.[54]

Dermatophytoses

Dermatoses are classified based on the primary location and can spread through direct contact or transmission of fomites. Tinea presents as pruritic, well-demarcated annular scaling plaques with surrounding erythema, with possible maceration. Figure 3 shows multiple examples of tinea pedis, as well as cutaneous maceration. Diagnosis is usually confirmed with a positive KOH preparation of a scale, which shows false negatives in only 15% of cases; a fungal culture can also be performed but may take weeks for results.[55] If a biopsy is performed, the pathologist looks for the presence of hyphae in the stratum corneum.[55] For dermatophyte treatment, localized tinea infections require topical antifungals such as terbinafine or clotrimazole.[55] Oral terbinafine or oral itraconazole are used for tinea infections that fail initial topical treatment or involve the hair, nails, or large surface areas.[55] Unfortunately named, tinea versicolor is a separate entity; it is caused by the lipid-dependent *Malassezia* yeast and is not a dermatophyte infection, as the organism does not metabolize keratin. Tinea versicolor may exhibit erythema but more often shows hypopigmented macules and patches.[56]

Cutaneous lupus erythematosus

About 80% of systemic lupus erythematous (SLE) patients develop cutaneous findings.[57] Cutaneous findings usually present in sun-exposed areas, classically as erythema of the malar portion of the face ("butterfly rash") with nasolabial sparing, as sunlight does not hit this skin. This eruption is reported in about 50% of patients at the time of diagnosis and is commonly termed the "red wolf face." The term *lupus,* Latin for wolf, was first coined in the 13th century to describe the wolf-bite appearance of the eruption, which may precede other SLE clinical manifestations by months or years. The red wolf face is usually slightly edematous and warm.[58,59] SLE can also become generalized and present in a variety of cutaneous morphologies, including a discoid eruption; in addition, constitutional clinical manifestations, arthritis, neurologic changes, serositis, photosensitivity, alopecia, and oral ulcerations are common.[60] The differential diagnosis of SLE includes dermatomyositis, scleroderma, photosensitivity reactions, and other autoimmune conditions. Biopsy and immunofluorescence also support the diagnosis. Dermatopathology can vary based on

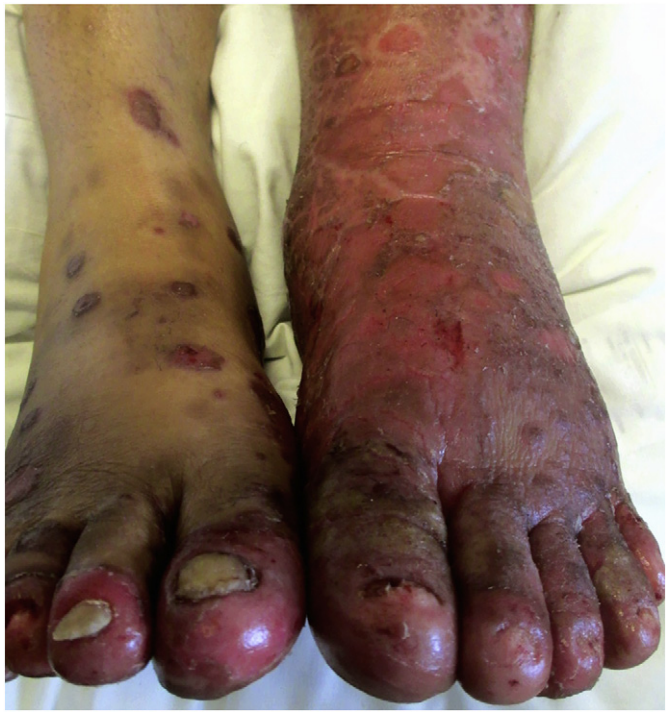

Fig. 3 Multiple annular well-defined erythematous plaques and cutaneous maceration of the distal legs and feet, representing bilateral tinea pedis.

the subtype of lupus. A positive lupus band test specifically shows immunoglobulin and complement at the dermal-epidermal junction, although cutaneous biopsy is not recommended over the more efficient serologic testing.[60] Cutaneous SLE should be treated with topical corticosteroids or calcineurin inhibitors; photosensitivity precautions should also be taken in these patients.[61] If the disease is severe or unresponsive to topical treatment, patients can be started on an oral antimalarial such as hydroxychloroquine.[61]

Dermatomyositis

Pathognomonic skin findings in dermatomyositis are the facial heliotrope eruption and Gottron papules. The heliotrope eruption is a red-to-violet eruption on the upper eyelids with or without eyelid edema.[62] Patients may also present with midface erythema, including involvement of the nasolabial folds. Clinically, interstitial lung disease, dysphagia, and polyarthritis are also associated with dermatomyositis, along with an increased risk of internal malignancy (eg, ovarian). Gottron papules are red-to-violet papules that occur symmetrically over the dorsal aspects of the metacarpophalangeal and interphalangeal joints. Patients may also have "mechanic's hands" with hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers.[63] Photoexposed areas, such as the face, chest, and upper part of the back, may demonstrate poikiloderma, often first presenting as a red-purple hue.[64]

For diagnosis, dermatomyositis requires a suggestive history, physical examination, and laboratory data. Serologic elevations in creatinine kinase, lactate dehydrogenase, aspartate aminotransferase (AST), and aldolase are common. Autoantibodies specific for dermatomyositis or polymyositis are anti-Jo-1 (histidyl-tRNA synthetase), anti-Mi-2, and anti-signal recognition particles.[65,66] Diagnosis can be made without muscle biopsy if the patient has a symmetrical proximal muscle weakness, elevated muscle enzymes/autoantibodies, and a pathognomonic eruption. Muscle biopsy, looking for perimysial inflammation and atrophy with CD4+ helper T-cell infiltration, aids the diagnosis in unclear cases.[67] Differentials ought to consider SLE, inclusion body myositis, drug-induced myopathy, hypothyoidism, myasthenia gravis, and motor neuron diseases. Treatment includes corticosteroids as first-line initial therapy, with progression to long-term steroid-sparing agents (methotrexate, azathioprine).[68] Skin manifestations are managed with sunlight avoidance.

Deep vein thrombosis

Deep vein thrombosis (DVT) refers to the formation of one or more blood thrombi, usually in the lower extremities. The Virchow triad (blood stasis, endothelial injury, and hypercoagulable state) highlights the predisposing risk factors.[69] The pathogenesis involves overactivation of the clotting cascade leading to fibrin-meshwork clots that are at risk for embolization (eg, pulmonary thromboembolism). Patients may present with unilateral leg swelling, pitting edema, pain, warmth, and erythema; however, many patients with a DVT present with nonspecific findings or are asymptomatic.

On physical examination, a common finding is a larger calf diameter (>3 cm difference). One meta-analysis reported that patients with a difference in calf diameter were twice as likely to have a DVT.[69] A Homans sign, or calf pain on passive foot dorsiflexion, is now considered an unreliable physical examination finding. Patients with a moderate-to-high probability of DVT should ideally undergo compression ultrasonography, whereas those with a low probability can be ruled out with a D-dimer assay.[70] The differential diagnosis for a DVT includes venous insufficiency, muscle strain/tear, popliteal cyst, lymphedema, and cellulitis. Patients are treated with acute anticoagulation (eg, unfractionated or low molecular weight heparin) and, if necessary, are chronically anticoagulated (eg, warfarin).

Stasis dermatitis

Stasis dermatitis represents a chronic inflammatory condition in patients with late stages of venous insufficiency.[71] Patients present with bilateral pruritic, scaly plaques on a background of pitting edema, erythema, and hyperpigmentation.[72] Severe cases can progress to lipodermatosclerosis or panniculitis of the lower portion of the legs; this can present as an indurated plaque associated with pain and a reddish discoloration.[71] Treatment includes gentle skin cleansing, emollients, wet dressings, and topical corticosteroids. Patients benefit from compression stockings.[72]

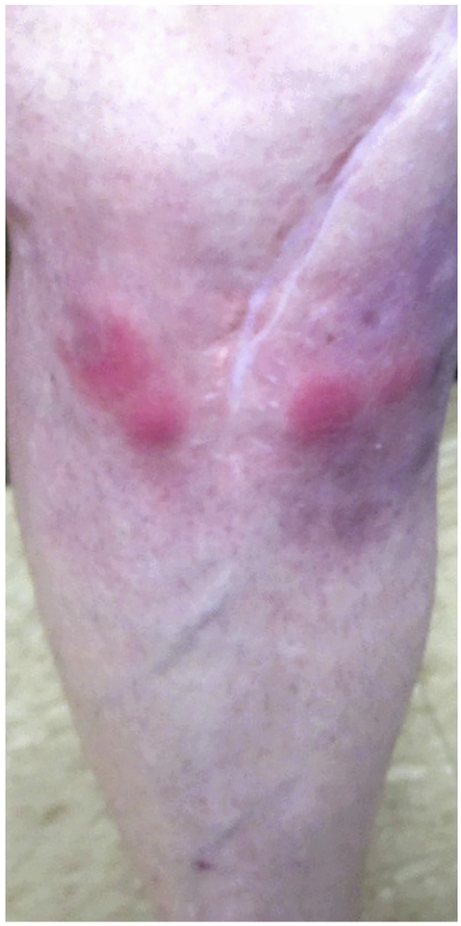

Fig. 4 Erythema nodosum: Three large erythematous nodules on a hyperpigmented background are seen on the distal leg.

Erythema nodosum

Erythema nodosum is a cutaneous manifestation of an acute painful panniculitis of the lower legs. The etiology of erythema nodosum is usually idiopathic, with one study showing a lack of etiology in 53% of patients.[73] Clinically, as seen in Figure 4, erythema nodosum often presents as erythematous, tender, raised, immobile nodules on the shins. There may be a prodrome of fever, arthralgias, and upper respiratory infection clinical manifestations before the appearance of cutaneous lesions.[74] The diagnosis is clinical, with a deep biopsy warranted in unclear cases; atypical cases include a location other than the shins, ulceration, immunosuppression, and nodules >5 cm. Histologically, erythema nodosum is a septal panniculitis without vasculitis.

The differential must consider a subcutaneous infection, malignant infiltrates, nodular vasculitis, and cutaneous polyarteritis nodosa. Erythema nodosum resolves spontaneously within several weeks, with secondary hyperpigmentation and bruising possible during the resolution phase. First-line treatment includes nonsteroidal antiinflammatory drugs (NSAIDs) or, if swift resolution is warranted, potassium iodide. Rest and compression therapy are suggested for all patients.[75] Systemic corticosteroids are reserved for patients who are unresponsive to first-line therapy or those with debilitating clinical manifestations.

Drug eruptions

Adverse drug reactions are commonly seen among patients on multiple medications and estimated to occur in up to 2% to 3% of inpatients.[76] Diffuse exanthematous drug eruptions represent 90% of drug eruptions,[77] and present mainly with erythematous, blanching macules and papules over the trunk and proximal extremities. The eruption usually starts on the trunk and spreads symmetrically to the extremities. Drug eruptions can be erythrodermic and mimic viral exanthems as "morbilliform" and "rubelliform" eruptions, although drug exanthems are more pruritic, confluent, and erythematous.[77] Other specific drug-induced exanthems include symmetrical intertriginous/flexural, urticaria/angioedema, vasculitis, drug-induced hypersensitivity syndrome (DIHS), erythema multiforme, and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

Symmetrical intertriginous/flexural drug eruptions, or "baboon syndrome," presents with well-demarcated patches of erythema in the buttocks and genital area, often involving one other intertriginous or flexural fold (eg, axilla).[78]

Urticaria has a pruritic, raised, erythematous, and circumscribed eruption that usually resolves in a few hours; the deeper dermis swelling of angioedema occurs alongside urticaria

in about 50% of cases and airway obstruction must be considered.

Drug-induced hypersensitivity syndrome, or DRESS syndrome, occurs with facial edema in half of cases.[79] Its morbilliform eruption rapidly progresses to a confluent, diffuse erythema with follicular accentuation, often involving more than 50% of the body surface area.[80]

The medical emergency of SJS/TEN presents with purpuric, erythematous macules with irregular borders that coalesce usually with diffuse erythema. Pain is the prominent symptom, often out of proportion to the physical examination. About 90% of cases have mucosal involvement that precede or follow the skin eruption.[81] The scalp, palms, and soles are rarely involved.[82] Lesions tend to begin on the face and thorax before spreading caudally in a symmetric pattern. Progression involves vesicle/bulla formation and skin sloughing.

Biopsy can support the diagnosis of a drug eruption and can be pursued if the diagnosis is unclear clinically.[83] Treatment of a drug eruption involves removal of the causative agent, and symptomatic treatment may be pursued using topical corticosteroids and antihistamines.[83] Burn-center care is needed for SJS/TEN patients.

Viral exanthems

Viral exanthems occur most commonly in children but can present in adults as well.[84] Major causative viruses include rubeola, rubella, roseola, and parvovirus B19; the incidence of each varies depending on the age.[84] The pathogenesis of a viral exanthem is through spread of the virus into the skin, where it causes a vascular reaction.[85] Clinically, viral exanthems are often nondescript and present as macules and papules that become generalized and confluent.[84,86]

Rubeola, morbilla, or the measles, has an erythematous, blanching maculopapular eruption that classically begins on the face and spreads caudally, with the palms/soles usually spared. With progression, the exanthema can turn nonblanched and the eruption may appear hemorrhagic.[87]

Rubella's exanthema presents similarly as it presents as pinpoint, pink papules that first appear on the face and travel caudally; however, rubella's spread is much more rapid (within 24 hours), does not darken/coalesce, and can also spread to the soft palate (Forchheimer spots).[88]

In infants, roseola's exanthema subitum normally arises after the high fever abates. Starting on the trunk/neck, blanching, nonpruritic macules and papules develop and spread to the face and extremities.[89] The late onset of the eruption may be confused with a medication allergy if antibiotics were administered for the fever.[90]

Parvovirus B19's erythema infectiosum occurs commonly in school-aged children, classically as an erythematous malar eruption with circumoral pallor (slapped cheek). Several days later, a reticular erythema develops on the trunk and extremities.[91,92] In adults, the eruption is less characteristic and may be confused with rubella.

The differential diagnosis of viral exanthems includes drug eruptions, toxic erythemas, SJS/TEN, and Kawasaki syndrome. Viral exanthems should be highly suspected in infants and pediatric patients; vaccination status should be addressed.[84] Biopsy is not indicated, but results can help rule out other conditions such as SJS/TEN. Treatment includes appropriate hydration and NSAIDs/acetaminophen.[84,86]

Toxic erythema

Toxic erythema is a group of disorders that involve a cutaneous reaction to a toxin.[85] There are four major types of toxic erythemas[85]:

- scarlet fever
- staphylococcal scalded skin syndrome (SSSS)
- Kawasaki syndrome
- toxic shock syndrome (TSS)

Toxic erythemas share a similar pathogenic mechanism, as each toxin acts as a superantigen that releases cytokines; these cytokines then result in the observed cutaneous and systemic findings.[85]

Scarlet fever is caused by a Type IV delayed reaction to a pyrogenic exotoxin from Group A streptococcus. The exanthem usually starts in the intertriginous regions of the groin or axilla and consists of a diffuse, blanching erythema as well as papules that give a "sandpaper" skin texture; a circumoral pallor and a strawberry tongue is also usually present.[93] The eruption rapidly spreads to the trunk and extremities, spares the palms/soles, and later desquamates. It often demonstrates petechial lines in the axillary folds and antecubital fossae (Pastia lines).[44] The patient can be treated as an outpatient with beta-lactam antibiotics.[94]

SSSS, also called Ritter disease, normally arises in infants/children and is a reaction to *Sta aureus* exfoliative toxins. The toxins act at the zona granulosa, causing cleavage of desmoglein 1 complex and formation of fragile bullae.[95] Skin has a positive Nikolsky sign, and the bullae concentrate at pressure points (buttocks, feet) and flexural areas. Mucous membranes are usually uninvolved but may be hyperemic. Scarring is rare. Biopsy is the test of choice for diagnosis.

Kawasaki syndrome is caused by an unknown immunologic trigger in children. It demonstrates a polymorphous eruption that usually begins as a perineal erythema with desquamation, progressing to macular or morbilliform exanthem of the trunk and extremities.[96] Kawasaki syndrome may also trigger a psoriasiform eruption in children.[97,98] Fever, mucositis, lymphadenopathy, and nonexudative conjunctivitis are normally present. Acute sunburn can be effectively treated with open wet dressings provided that it is not severe. Treatment is with either aspirin or intravenous immunoglobulin.[99]

TSS is mainly caused by MSSA, although the rates of MRSA producing the toxic shock syndrome toxin (TSST) are increasing.[100] The skin, resembling widespread sunburn, usually presents as erythroderma and with generalized, red macules that can involve the palms/soles. Mucosal involvement can cause vaginal or oral hyperemia and conjunctival-scleral hemorrhage.[101] The eruption can progress to pruritic macules and papules with desquamation of the palms/soles. Nail and hair may occur 1 to 2 months after illness onset.[102] TSS should be managed inpatient with either a penicillinase-resistant penicillin or vancomycin if MRSA is suspected.[103,104]

Red man syndrome

Red man syndrome (RMS) is a well-documented side effect of vancomycin, which occurs mainly with parenteral administration. RMS is a pseudoallergic drug reaction that occurs when vancomycin activates mast cells, which release vasoactive mediators such as histamine; unlike an allergic reaction, RMS can occur with the first administration of vancomycin and is not IgE mediated. RMS presents with diffuse pruritic erythema, which predominantly affects the face, neck, and trunk. Studies show that the risk of RMS is rate-dependent, and vancomycin should be infused at a slow rate of 10 mg/min to avoid RMS.[105,106] Prevention of RMS can be done using oral H_1 antihistamines, especially if rapid infusions are required in the emergency setting.[107] Treatment of RMS is dependent on the severity of the reaction, but in all cases vancomycin infusions should be halted at the presentation of RMS. Asymptomatic RMS is self-resolving. Symptomatic patients should be treated with diphenhydramine and ranitidine. In symptomatic patients without chest pain, muscle spasms, or hypotension, after the clinical manifestations resolve, vancomycin can be restarted at half the original rate.

Erythroderma

Erythroderma is defined as a rare condition with erythema involving $\geq$ 90% of the total body surface area.[108] There are four major etiologies of erythroderma[85]:

- primary dermatosis (eg, psoriasis)
- drug reactions (eg, RMS)
- malignancy (eg, Sézary syndrome)
- idiopathic

Diagnosis is primarily clinical, with patients presenting with a pruritic, diffuse generalized erythema with possible scaling; skin exfoliation usually occurs within a week of the erythema.[85,109] A skin biopsy can determine the underlying etiology but is usually nonspecific. Determining the etiology can be difficult, as the erythroderma can replace signs of the underlying etiology on clinical examination or biopsy. Certain specific signs include severe scaling (psoriasis), salmon pink coloration with islands of sparing (pityriasis rubra pilaris), keratoderma (Sézary syndrome or pityriasis rubra pilaris), bullae (immunobullous disorder), and nail pitting (psoriasis). Many patients have leukocytosis.

Patients with chronically progressing erythroderma over weeks to months and generalized lymphadenopathy should have flow cytometry and T-cell clonality studies done to rule out Sézary syndrome.[110] Primary treatment involves possible inpatient hospitalization and supportive care; patients with erythroderma are prone to temperature instability, fluid shifts, and secondary infections from skin barrier breakdown.[109] Patients should also be treated with low or midpotency topical steroids, wet dressings, and antihistamines.[108] If the etiology is unknown and patients are unresponsive to topical therapy, systemic corticosteroids are a treatment option, although the evidence for steroid efficacy is limited to case studies.[85,110]

Sunburn

Sunburns, a subtype of superficial burns, are acute delayed inflammatory responses, most often caused by ultraviolet B radiation (290-320 nm).[111] Although the sun is mainly a source of UVA, with 95% of radiation reaching earth in the UVA range, UVB causes more than 80% of the erythema-causing energy.[112] DNA photodamage by way of pyrimidine dimers and 6-4 pyrimidine-pyrimidone photoproducts triggers the inflammatory response as well as UVB-mediated delayed pigmentation.[113] Examination includes painful erythema, blistering, and possible vesiculation/bullae formation. Histologically, the epidermis contains "sunburn cells," or apoptotic keratinocytes, along with spongiosis and parakeratosis.[114] The differential includes cellulitis, chemical/thermal burns, and exfoliative dermatitis (eg, SSSS).

Burns

Burns are traumatic cutaneous injuries by heat, electricity, friction, radiation, or chemicals. Superficial burns involve only the epidermis. These are painful, blanchable, red patches that do not blister or scar.[115] These burns usually heal within a week and are not included in measurement of total body surface area burn assessment (rule of nines). Partial-thickness burns involve some of the dermis and are painful, red, weeping patches that blanch. These lesions can take 1 to 3 weeks to heal, usually without functional impairment or scarring.[116] Full-thickness burns extend through the entire dermis and often present with an eschar. These burns are usually anesthetic, with white/leathery gray skin and areas of charred necrosis. Scarring and wound contracture occur without surgical intervention. Full-thickness burns should be referred to specialized centers, as should superficial/partial-thickness burns in functionally sensitive areas (eg, face, hands, genitalia).[117] Minor burns are managed with cool saline-soaked gauze, topical antibiotics, aloe, and close followup for signs of full-thickness burn development.

Red scrotum

Candidal intertrigo (diaper dermatitis) is one cause of a red scrotum. It usually involves a uniformly red scrotum that includes the skin folds (in contrast with irritant diaper dermatitis).[118] Atopic dermatitis may also affect scrotal skin. This chronic inflammation may lead to the "thick and leathery," lichenified scrotum. Dermatophytes causing tinea cruris (jock itch) usually spare the scrotum and cause itchy, well-demarcated groin patches. This does not preclude a red scrotum, as the bystander trauma from scratching the tinea cruris can irritate scrotal skin.

There is also the rare red scrotum syndrome, a persistent scrotal erythema—most often on the anterior portion—associated with hyperalgesia, burning, and itching. This condition most often affects older white men, and its etiology is unknown. Hypotheses include corticosteroid-induced rebound vasodilation or a rosacea-like dermatosis.[119,120] Limited data have suggested doxycycline as an effective treatment.[121] Dermatitis of the scrotum has been suggested as a cause of infertility due to dysfunctional temperature regulation, making effective management of even greater importance.[122]

Red vulva

The most common cause of a red vulva is candidosis, although other systemic conditions can manifest on the vulva such as atopic dermatitis and psoriasis. The most prominent symptom of candida vulvovaginitis, also known as a yeast infection, is pruritus, with often little to no vaginal discharge. Lichen simplex chronicus can be primary or secondary to pruritic conditions such as candida vulvovaginitis, atopic dermatitis, or even neuropathy.[123] Lichen simplex chronicus is a manifestation of the itch-scratch cycle with development of lichenified plaques. Although topical corticosteroids are the mainstay of treatment, a small randomized trial also supported the use of topical aspirin.[124] As with scrotal skin, tinea cruris usually spares the labia majora, although the area may be irritated by scratching. Similarly, tinea versicolor rarely causes asymptomatic, well-demarcated pink macules/patches on the vulva with scale, but it should only be considered when other chest and back lesions are present.[125]

Red palms

Dermatophytes can also target the hand as tinea manuum, often from *Trichophyton rubrum.* Patients often present with annual, erythematous plaques on the dorsal surface of the hand and/or hyperkeratosis and erythema of the palms.[126] Because tinea manuum is often unilateral and commonly occurs alongside tinea pedis, it has been described as "two-feet, one hand syndrome."[127]

Postinflammatory erythema

Postinflammatory erythema (PIE) is a relatively new term in the dermatology lexicon that describes the phenomenon of pink-to-red discoloration after an inflammatory acne lesion, although any resolving cutaneous inflammatory process may have residual erythema.[128] These lesions often arise in patients with lighter skin types (I-III) as discrete erythematous macules. Darker skin types often experience postinflammatory hyperpigmentation. Intense pulsed light laser therapy has shown efficacy in resolving PIE in limited retrospective studies.[129]

Phototoxic reactions

Phototoxic reactions are polymorphous light eruptions on sun-exposed skin due to medications. This occurs when drugs (eg, hydrochlorothiazide, NSAIDs) absorb radiation from the sun (usually UVA), leading to chemical reactions, reactive oxygen species, and inflammation that causes cellular damage.[130] The drug amount is usually systemic and requires a dose-dependent concentration to cause the phototoxicity only on exposed skin. Patients present with exaggerated sunburns with or without blistering (epidermal degeneration, dermal edema, vasodilatation, and mononuclear infiltrate) minutes to hours after light exposure.[130] This is in contrast to the cell-mediated photoallergic reaction, a type of allergic dermatitis in which a photosensitizing drug previously activated by light serves as an allergen. Later photoallergic episodes of drug use and light exposure lead to a dermatitis involving exposed and unexposed skin usually after 24 hours.[131] A thorough review of medications is essential to diagnosis.

Conclusions

Consideration of the pathophysiology behind red color is valuable in helping clinicians comprehend and treat the red diseases. The vasodilatory response controls blood flow and dermal concentration. Chemical mediators, such as histamines, prostaglandins, and bradykinins, relax arteriolar smooth muscle, expand the blood vessel diameter, and increase flow. This response is under local or distance control, from the red mark of a slapped wrist or inflamed comedo to the widespread exanthema of a drug-induced hypersensitivity reaction. Blood flow and its photoreflective properties within the visible dermis determine red color. Changes in blood's visual throughout the skin usually occurs due to inflammation, hemorrhage, or vessel malformations. Red skin disorders contain a wide group clinico-pathologically and extend beyond irritation. An understanding of blood's role in these disorders equips clinicians to generate differential diagnoses through the lens of pathophysiology. Coupled with clinical experience, this integration promotes optimal patient care.

Conflict of interest

All four authors report no conflicts of interest.

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